REMARKS

Claim 61 has been amended to recite SEQ ID NO. 2, which sets forth the presently claimed OPGL sequence, and claims 65 and 67 have been grammatically amended.

Claims 88 and 89 have been added, support for which may be found in the original claims and the Specification (pages 16-19).

The claims have been amended to more clearly describe the present invention. No new matter has been added.

1. Double Patenting

The double patenting rejection imposed in the Office Action of January 31, 2005 has been maintained. In this Office Action, the Examiner has recognized that Applicants will address the issue upon the indication of allowable subject matter.

2. Claim Rejections under §112, First Paragraph - Enablement

The Examiner has rejected all of the pending claims as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse.

The Examiner sets forth several grounds for imposing the enablement rejections (Office Action, pages 3-7). Below, Applicants address each aspect of the rejection.

2(a) Summary of the Rejections and Applicant's Response

Before addressing the details of the Examiner's rejections below, it is important to first have a view of the "big picture" of the present invention. The Examiner's enablement and written description rejections

are typical of biotech inventions that are directed to the discovery of a protein sequence with biological/pharmaceutical properties, wherein an applicant seeks to claim the protein and some scope of modifications to that protein. The USPTO will typically reject broad claims to such "modifications" on the basis that even small changes to a protein sequence can significantly alter or destroy the biological/pharmaceutical activity of that protein.

The present invention is a different type of case. Applicants do not allege to be the first to discover the sequence of OPGL, nor do the Applicants allege to have first discovered the biological activity of the protein. These aspects are already known in the art. Applicants have, rather, surprisingly discovered that it is feasible to immunologically target self-OPGL in order to reduce/abolish bone loss in the condition/disease states where such treatment is desirable. Applicants' invention, therefore, is focused on immunogenic or vaccine activity of modified OPGL molecules which have been modified to promote an immune response in a mammal, specifically an immune response directed against the modified OPGL which is cross-reactive with the mammal's self OPGL. Applicants have provided both a long disclosure and numerous examples in the Specification which, combined with the high level of skill in the art, Applicants submit well support the present claims and well teach those of skill in the art how to practice the claimed invention.

The Examiner has rejected all of the claims for alleged lack of enablement and alleged lack of written description. The Applicants believe that the Examiner has failed to properly substantiate any legally sufficient *prima facia* case in order to reject the present claims. While the Examiner's rejections seem to be long in detail, the Office Action is glaringly void of <u>any evidence</u> which substantiates the rejections. Without any such evidence, the rejection essentially amounts to a broad allegation that the claims are "too broad." But such a broad allegation does not amount to a legally sufficient *prima facia* case to reject the claims.

The Examiner is reminded that "the Examiner has the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. There is a strong presumption that an adequate written description of the claimed invention is present in

the Specification as filed". (See the "Guidelines for Examination of Patent Applications under 35 USC 112, Paragraph 1, Written Description Requirement, Fed.Reg.Vol. 66, No. 4, 1099, 1105 (January 5, 2001).

Applicants submit that in the present case the Examiner has not started with a "strong presumption" of an adequate written description and has not presented any evidence of why a person skilled in the art would not recognize that the specification provides support for the present claims. The Examiner is reminded that the guidelines go on to state that "The objection of an original claim for lack of written description should be rare."

In a similar manner, MPEP §2164 sets forth the clear initial burden on the Examiner before rejecting an application for lack of enablement. In order to properly establish a *prima facia* case for lack of enablement, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth and accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is consistent with the contested statement. Otherwise, there would be no need for the Applicant to go to the trouble and expenses supporting this presumptively active disclosure." *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971).

Applicants assert, therefore, that the Examiner has failed to establish a *prima facia* case for lack of enablement or lack of sufficient written description, because the Examiner has failed to recognize that the present specification is "presumptively" enabling and sufficient, and the Examiner has failed to rebut that presumption with any evidence or scientifically based reasoning.

2(b) The Number of T-Cell and B-Cell Epitopes

On page 5 of the Office Action, the Examiner contends that the Specification fails provide sufficient guidance regarding the minimum and maximum numbers of T-cell and B-cell epitopes required for the presently claimed modified OPGL polypeptides to promote an immune response.

2(b)(i) *The Minimum Number of T-Cell and B-Cell Epitopes*

With respect to the minimum number of epitopes, the Specification and the claims dictate that the modified OPGL polypeptides of the invention contain at least one T-cell and at least one B-cell epitope. In particular, the Specification recites that, since OPGL is a self-protein, normal people do not mount an immune response against unmodified OPGL (page 13, lines 2-6). A novel and non-obvious aspect of the present invention is to provide a method for promoting an immune response against naturally occurring OPGL (*i.e.* unmodified OPGL) by the presentation of the presently claimed modified OPGL polypeptides to a mammal's immune system. Applicants disclose that, in order to trigger an immune response directed against OPGL, OPGL polypeptides must be modified with at least one T-cell epitope (Specification page 16, line 33).

The Specification further teaches that the introduction of T-cell epitopes into OPGL causes a mammalian immune system to mount a B-cell response against the OPGL portion(s) of the presently claimed modified OPGL polypeptides. The Specification discloses that the B-cell antibodies which recognize OPGL sequences of the presently claimed modified OPGL polypeptides cross react with naturally occurring OPGL (*i.e.* unmodified OPGL) (page 16, lines 1-27). There must therefore be at least one B-cell epitope in the claimed modified OPGL polypeptides to trigger an immune response against OPGL.

Based on the points discussed above, Applicants submit that the Specification provides sufficient guidance that at least one T-Cell epitope and at least one B-Cell epitope is required in the currently claimed modified OPGL polypeptides. The Specification therefore fully enables a person of ordinary skill in the art (POSITA) to make and use the minimum number of epitope aspect of the presently claimed invention without undue experimentation.

2(b)(ii) *The Maximum Number of T-Cell and B-Cell Epitopes*

By way of reminder, Applicants point out that it is unnecessary to recite in the Specification what is well known in the art. Accordingly, Applicants submit that it is unnecessary to determine a precise

maximum number of T-cell and B-cell epitopes in order for the Specification's teachings to enable a POSTIA to practice the presently claimed invention without undue experimentation.

It is well known in the art that the inclusion of multiple copies of a single epitope in a protein can increase the affinity by which an antibody which specifically binds that epitope binds the entire protein. Well known examples here include "tagging" constructs for immunoprecipitation assays designed to test for protein-protein interactions. A POSITA recognizes that the optimal epitope number can vary, and has the knowledge and skill to efficiently identify that number.

Moreover, U.S. Patent Nos. 5,229,490 and 5,614,194 are exemplary publications which show that it is well known in the art how to practice effective immunizations based on the use of multiple antigen peptides and vaccination constructs, respectively. Applicants have submitted copies of these patents with this response.

As a final point, Applicants point out that the Examiner has failed to present any evidence showing a need to set a limit as to the number of epitopes for the efficient practice of the presently claimed invention. In light of the Examiner's failure to meet his evidentiary burden and the knowledge and skill of a POSITA in the field, as well as the state of the art, Applicants submit the Specification fully enables a POSITA to practice the multiple epitope aspect of the presently claimed invention without undue experimentation.

2(c) The Length and Identity of B-Cell Epitopes

The Examiner mistakenly contends that the Specification fails to teach the identity and length of the B-cell epitopes contained in the presently claimed modified OPGL polypeptides (Office Action, page 5). The Specification in fact teaches that the whole OPGL sequence can be used as the B-cell epitope sequence (page 17, lines 6-17), and Applicants disclose OPGL's 318 amino acid sequence in SEQ ID NO: 2.

The Specification further teaches that subsequences of OPGL may be used in the claimed polypeptide. In particular, the Specification teaches that, based on OPGL's structural relationship with TNF-α,

OPGL amino acids 171-193, 199-219, 222-247, 257-262 and 286-317 of SEQ ID NO: 2 may be used in the presently claimed modified OPGL polypeptides (page 28, lines 23-33); and also that the active site of OPGL, amino acids158-316, of OPGL also may be used (Example, page 58).

It is, moreover, well known in the art that most polypeptides of just a few amino acids can be used to raise an immunogenic response (either directly or by coupling with an adjuvant). In addition, it is well known that, based on entropics, proteins form globular structures in which hydrophobic amino acid side chains are buried in the center (and thereby shielded from energetically unfavorable interactions with the aqueous medium); whereas hydrophilic amino acid side chains are positioned on the surface of a protein. There are several computer programs for mapping the hydrophobicity of proteins (in simplistic terms, these programs determine the number of hydrophobic amino acids present in a rolling window of several amino acids). A POSITA would therefore have the skill and knowledge to efficiently make and use a hydrophobicity map of OPGL for identifying stretches of amino acids of low hydrophobicity within OPGL that are likely to be presented on the surface (and therefore immunogenic) for use in the presently claimed invention.

Based on the aforementioned points, Applicants submit that the Specification, in combination with the knowledge and skill of a POSITA (which is high in the biotechnology field), provides sufficient guidance regarding the identity and length of the B-cell epitope to be used in the presently claimed invention to allow a POSITA to practice the present invention without undue experimentation.

2(d) The Parts of OPGL that May Be Used to Generate the Immune Response

On Page 6 of the Office Action, the Examiner contends that the Specification does not teach which parts of OPGL can be used to generate the immune response. In general, Applicants submit that the discussion presented in 2(b) addresses this concern as well. Applicants point out that the Specification teaches it is logical to use OPGL amino acids 158-316 of SEQ ID NO: 2 because these amino acids comprise the active site of OPGL. Antibodies directed against the active site have the potential to both block OPGL function by steric interference with the active site as well as to reduce the concentration of OPGL in the body by the clearing effects of an autoimmune response directed against OPGL.

In contrast, antibodies directed against OPGL sequences outside of the active site would engage the clearing autoimmune response, but would unlikely be capable of sterically blocking OPGL activity. It follows that both active site OPGL sequences and OPGL sequences outside the active site are attractive for use in the present invention.

In light of the foregoing discussion, Applicants submit that each and every aspect of the Examiner's concerns regarding the enablement requirement have been addressed and refuted. It is urged that the disclosure Applicants have provided in the Specification enables a POSITA to make and use the presently claimed invention without undue experimentation. Applicants therefore respectfully request the rejection be withdrawn.

3. Claim Rejections under §112, First Paragraph – Written Description

The Examiner has rejected all of the pending claims as allegedly failing to comply with the written description requirement. Applicants respectfully traverse.

Here, the Examiner makes broad and inaccurate generalizations about the Specification's disclosure:

> "There is no disclosure of complete or partial structure, physical and/or chemical properties, or methods of making the claimed product." (Office Action, page 8).

In regards to the B-cell epitopes of the presently claimed invention, Applicants disclose that the entire amino acid sequence of OPGL, set forth in SEQ ID NO: 2, is useful. In the Specification, Applicants further indicate that subsequences that can be used in the presently claimed modified OPGL polypeptides include amino acids 171-193, 199-219, 222-247, 257-262 and 286-317 of SEQ ID NO: 2 (page 28, lines 23-33); and that the active site of OPGL, amino acids158-316, of OPGL may also be used (Example, page 58).

In regards to the T-cell epitopes useful in the presently claimed invention, the Specification defines T-cell epitopes as peptides that are able to bind an MHC molecule and stimulate T-cells in an animal species (page 16, lines 14-16). The Specification goes on to describe preferred embodiments of T-cell epitopes, including both natural and artificial sequences such as the P2 and P30 tetanus toxin epitopes, the diphtheria epitope, the HA epitope, the CS epitope and the PADRE epitopes, which are useful in the presently claimed invention (Specification, pages 24-25).

The Specification further teaches that OPGL polypeptides may be modified to contain T-cell epitopes either by inserting a complete T-cell epitope sequence into a OPGL sequence, or by making amino acid changes to certain OPGL amino acids so that a T-cell epitope is created. The cloning and mutagenesis techniques involved in making these modifications, whether for the modification of OPGL to carry a single or multiple T-cell epitope(s), are well known in the art.

Applicants submit that the Specification's disclosure of multiple representatives of each currently claimed generic element indicates Applicants had possession of the presently claimed invention at the time of filing. It is therefore respectfully requested that the written description rejection be withdrawn.

4. Claim Objections

The Examiner has objected to claim 65 for labeling as formula I a formula that does not correspond to formula I of claim 1. Applicants have amended claim 65 to recite formula II, thereby obviating the rejection.

In view of the foregoing amendments and remarks, Applicant believes the present application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application; the Examiner is respectfully requested to contact Leonard R. Svensson (Reg. No. 30,330) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a three (3) month extension of time for filing a reply in connection with the present application, and the required fee of $1020.00 is attached hereto. Please charge Deposit Account 02-2448 in the amount of $1020.00.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____

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